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PATENT SPECIFICATION

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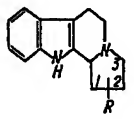
COMPLETE SPECIFICATION

Indolo-Indolizine Compounds

We, N.V. KONINKLIJKE PHARMACEUTISCHE FABRIEKEN V/H BROCADES-STHEEMAN & PHARMACIA, a Dutch Body Corporate, of Stationsweg 33, Meppel, Holland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to therapeutically useful indolo-indolizines and acid addition salts thereof.

It has been found after research and experimentation that indolo-indolizines of the general formula:



I

(wherein R represents hydrogen or an alkyl group containing up to five carbon atoms) and acid addition salts thereof are therapeutically active compounds useful as sedatives. For therapeutic purposes they may be employed as such or in the form of non-toxic acid addition salts, i.e. salts, which are not harmful to the animal organism when used in therapeutic doses, derived from inorganic acids such as the hydrohalic acids (e.g. hydrochloric and hydrobromic acids) and organic acids such as oxalic, maleic, fumaric, citric and tartaric acids. Compounds of outstanding importance are those in which R represents a methyl group and especially the compound wherein the methyl group is in the 2-position of the indolizine ring, and non-toxic acid addition salts thereof.

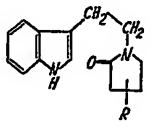
According to the present invention there are provided pharmacceutical preparations containing, as active ingredient, at least one indolo-indolizine compound of formula I, or non-toxic acid addition salt thereof, in association with a pharmacologically acceptable carrier, which is either a solid or semi-solid substance, or a liquid, the preparations in the latter case being in the form of a syrup or elixir or in the form of a sterile liquid suitable for use by injection. By the term "sterile" as used in this specification and accompanying claims is meant a liquid that has been made free from all bacteria and their spores by any suitable method of sterilization such as by physical or chemical means. The preparations for oral administration are preferably in the form of tablets, pills, powders, and capsules including the substance. The tablets and pills may be formulated in manner known *per se* with one or more pharmacologically acceptable solid diluents or excipients such as lactose or starch, and include materials of a lubricating nature such as calcium stearate. Capsules made of absorbable material, such as gelatin, may contain the active substance alone or in admixture with a solid or liquid diluent. Liquid preparations may be in the form of syrups or elixirs of the active substance in water or other liquid medium commonly used for making orally acceptable pharmaceutical formulations, such as liquid paraffin, or a syrup or elixir base. The active substance may also be made up in a form suitable for parenteral administration, i.e: as a suspension or emulsion in sterile water or organic liquid usually employed for injectable preparations, for example vegetable oil such as olive oil, or a sterile solution in an organic solvent. The amount of active substance in the pharmaceutical preparations may be varied, but should be sufficient to enable a quantity of 10 to 100 mg. of active substance to be administered daily with little, or no, inconvenience to the patient. Such a quantity is generally suitable for clinical purposes, and is preferably given by means of tablets containing 10 to 25 mg. of active substance.

The indolo-indolizines of formula I in which R represents an alkyl group are hitherto un-

[*Price 4s. 6d.*]

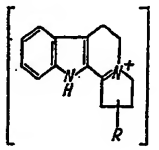
known compounds and, as such, form a feature of the invention.

According to another feature of the invention, the indolo-indolizines of formula I are prepared by the process which comprises reacting tryptamine with an ester of a γ-halogenobutyric acid (the halogen substituent being bromine or chlorine, preferably the former), which may carry on one of the carbon atoms of the trimethylene chain an alkyl substituent containing up to five carbon atoms, and cyclising the resultant indolylethylpyrrolidone of the formula:



II

(wherein R is as hereinbefore defined) by the method of Bischler and Napieralski using, for example, phosphorus oxychloride as cyclising agent, to a quaternary ammonium compound of the formula:



III

(wherein X represents the anion of a monobasic acid, and R is as hereinbefore defined) and reducing the quaternary ammonium compound thus obtained by treatment with sodium borohydride to an indolo-indolizine of formula I.

The reaction of tryptamine with an ester (preferably an alkyl ester) of a γ-halogenobutyric acid of the formula

$$Hal—CH_2—CH_2—CH_2—COOR_1$$

(R_1 being any suitable organic radical and Hal representing bromine or chlorine), optionally carrying an alkyl substituent on the trimethylene chain, is preferably effected in an inert organic solvent, such as xylene or toluene, and in the presence of a basic condensing agent such as potassium carbonate. When the aforesaid acid carries an alkyl substituent on the α, β or γ-carbon atom the product obtained is one in which R in formula II is an alkyl group.

The bromo- and chloro-butyrates employed as starting materials may be prepared by methods described in the literature, or by application of those methods.

The following Example illustrates pharmaceutical compositions according to the invention.

EXAMPLE I.

Tablets are prepared consisting of:

2,3,5,6,11,11b - hexahydro - 2-methyl - 1H - indolo[3,2 - g]-indolizine (suitably in the form of a non-toxic acid addition salt)	10 mg.
lactose	135 mg.
starch	1150 mg.
calcium stearate	5 mg.

The materials are thoroughly mixed and then treated with an aqueous gelatin solution containing 10% by weight of gelatin. The resulting mass is granulated and passed through a No. 10-mesh screen. The mixture is dried overnight at 40°C. The granules are then sieved through a No. 20-mesh screen and compressed into tablets weighing 250 mg. each.

The following Examples, in which the percentage yields are related to the theoretical yield, illustration the preparation of indolo-indolizine compounds of formula I.

EXAMPLE II.

2,3,5,6,11,11b - Hexahydro - 2 - methyl-1H - indolo[3,2 - g] - indolizine.

(a) A mixture of 11.2 g. of tryptamine, 12.6 g. of ethyl 4 - bromo - 3 - methylbutyrate, 8 g. of potassium carbonate, a small crystal of potassium iodide and 200 ml. of xylene are boiled under reflux for 48 hours. The mixture is then cooled and undissolved inorganic salts removed by filtration. The filtrate is concentrated by distillation of the solvent under reduced pressure. The residue solidifies upon cooling. Crystallisation from ethyl acetate yields 14 g. (82%) of 1 - [2 - (3 - indolyl)-ethyl] - 4 - methylpyrrolid - 2 - one, melting at 111—112°C.

Analysis: Calculated for $C_{15}H_{18}N_2O$: C, 74.35%, H, 7.49%, N, 11.57%
Found: C, 74.59%, H, 7.29%, N, 11.40%

(b) 6. g. of 1 - [2 - (3 - indolyl)ethyl] - 4-methylpyrrolid - 2 - one are mixed with 40 ml. of phosphorus oxychloride and 25 ml. of xylene and heated at a temperature of 130—140°C. for 1½ hours. Excess of phosphorus oxychloride and most of the xylene are removed by distillation under reduced pressure. The residue is treated with ethanol and neutralised with a sodium hydroxide solution. 2 g. of sodium borohydride are then added and the mixture is left standing overnight. A further quantity of 1 g. of sodium borohydride is then added. The solution is boiled under reflux for 1 hour, concentrated under reduced pressure, and water and ether are added to the residue. The ethereal solution

is separated, washed and dried with sodium sulphate. After filtration, an ethereal solution of oxalic acid is added causing the oxalate of 2,3,5,6,11,11b - hexahydro - 2 - methyl - 1H-indolo[3,2 - g]indolizine to precipitate. The salt is crystallised from a mixture of methanol and acetone, yielding 1.4 g. of product, melting at 180—182.5°C.

Analysis: Calculated for $C_{17}H_{20}O_4N_2$: C, 64.54%, H, 6.38%, N, 8.86%
Found: C, 64.56%, H, 6.49% N, 8.71%

The ethyl 4 - bromo - 3 - methylbutyrate used as a starting material can be prepared by condensing acetaldehyde with cyanacetamide. β-Methylglutaric acid is obtained upon saponification. The corresponding anhydride is prepared by heating with acetic anhydride. Treatment of the anhydride according to the procedure described by Cason (J. Org. Chem. *14*, 152 (1949)) yields monomethyl β-methylglutarate. The silver salt of the last-mentioned compound is converted into ethyl 4-bromo - 3 - methylbutyrate using a Hunsdiecker reaction as described by Marks and Polgar (J. Chem. Soc. *1955*, 3855).

EXAMPLE III.

2,3,5,6,11,11b - Hexahydro - 1 - methyl-1H - indolo[3,2 - g] - indolizine.

Following the procedure of Example II but substituting an equivalent amount of ethyl 4 - bromo - 2 - methylbutyrate for the ethyl 4 - bromo - 3 - methylbutyrate in step (a), there is obtained 1 - [2 - (3 - indolyl)ethyl] - 3 - methylpyrrolid - 2 - one, melting point 102—105°C. after crystallization from ethyl acetate. Yield 55%.

Analysis: Calculated for $C_{15}H_{18}N_2O$: C, 74.35%, H, 7.49%, N, 11.57%
Found: C, 73.73%, H, 7.39%, N, 11.72%

From the pyrrolidone, 2,3,5,6,11,11b-hexahydro - 1 - methyl - 1H - indolo[3,2 - g]-indolizine is prepared by cyclisation and reduction following the procedure of Example II(b). Its oxalate can be purified by crystallisation from a mixture of acetone and methanol; melting point of the oxalate, 205—209°C.

Analysis: Calculated for $C_{17}H_{20}O_4N_2$: C, 64.54%, H, 6.38%, N, 8.86%
Found: C, 64.93%, H, 6.10%, N, 8.87%

The ethyl 4 - bromo - 2 - methylbutyrate used as a starting material can be prepared by reacting butyrolactone with ethyl acetate under the influence of sodium to yield α-acetylbutyrolactone. The remaining hydrogen atom on the α-carbon atom is replaced by a methyl group by treatment with sodium followed by reaction of the sodium compound with methyl bromide. The α - methyl - α - acetylbutyrolactone obtained is subjected to acid-cleavage, yielding α - methyl - butyrolactone. The latter compound is converted into ethyl 4 - bromo-2 - methylbutyrate according to the procedure described in Houben Weil, Methoden der Organischen Chemie, *8*, 528.

EXAMPLE IV.

2,3,5,6,11,11b - Hexahydro - 3 - methyl, 1 H- indolo[3,2 - g] - indolizine.

Following the procedure of Example II but substituting an equivalent amount of ethyl 4-bromovalerate for the ethyl 4 - bromo - 3-methylbutyrate in step (a), there is obtained 1 - [2 - (3 - indolyl)ethyl] - 5 - methylpyrrolid - 2 - one, melting at 136—137°C. after crystallisation from ethyl acetate and acetone. Yield 82%.

Analysis: Calculated for $C_{15}H_{18}N_2O$: C, 74.35%, H, 7.49%, N, 11.57%
Found: C, 74.33%, H, 7.44%, N, 11.61%

From the pyrrolidone, 2,3,5,6,11,11b-hexahydro - 3 - methyl - 1H - indolo[3,2 - g]-indolizine is prepared by cyclisation and reduction according to the procedure described in Example II(b). Its hydrochloride melts at 244—246.5°C.

The ethyl 4 - methyl - 4 - bromobutyrate used as a starting material can be prepared by boiling starch or cane sugar with concentrated hydrochloric acid yielding levulinic acid as described in Organic Synthesis, Coll. Vol. I, 335. The acid is reduced and cyclised to form 4 - methylbutyrolactone. The lactone is converted into ethyl 4-bromovalerate using the procedure described in Houben Weil, Methoden der Organischen Chemie (*loc. cit.*).

EXAMPLE V.

2,3,5,6,11,11b - Hexahydro - 1H - indolo-[3,2 - g] - indolizine.

Following the procedure of Example II but substituting an equivalent amount of ethyl 4-bromobutyrate for the ethyl 4 - bromo - 3-methylbutyrate in step (a), there is obtained 1 - [2 - (3 - indolyl)ethyl] - pyrrolid - 2 - one, melting at 132.5—134.5°C. after crystallisation from ethyl acetate and ethanol. Yield 55%.

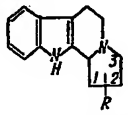
Analysis: Calculated for $C_{14}H_{16}N_2O$: C, 73.65%, H, 7.06%, N, 12.27%
Found: C, 73.56%, H, 7.21%, N, 12.35%

From the pyrrolidone, 2,3,5,6,11,11b-hexahydro - 1H - indolo[3,2 - g] - indolizine is prepared by cyclisation and reduction according to the procedure described in Example II(b). The free base melts at 169.5—171.5°C. after crystallisation from methanol and water. Yield 43%.

The ethyl 4 - bromobutyrate used as a starting material is prepared from commercially available butyrolactone according to the method described in Houben Weil (*loc. cit.*).

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation containing, as active ingredient, at least one indolo-indolizine compound of the general formula:



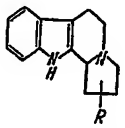
(wherein R represents hydrogen or an alkyl group containing up to five carbon atoms), or non-toxic acid addition salt thereof, in association with a pharmacologically acceptable carrier which is either a solid or semi-solid substance, or a liquid, the preparation in the latter case being in the form of a syrup or elixir or in the form of a sterile liquid suitable for use by injection.

2. Pharmaceutical preparations according to claim 1 wherein the pharmaceutical carrier is a solid and the composition is in the form of a powder or tablet.

3. Pharmaceutical preparations according to claim 1 or 2 wherein the preparation is in the form of a tablet containing 10 to 25 mg. of indolo-indolizine compound.

4. Pharmaceutical preparations containing an indolo-indolizine compound of the formula defined in claim 1, or non-toxic acid addition salt thereof, substantially as hereinbefore defined with especial reference to Example I.

5. Indolo-indolizine compounds of the formula:

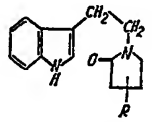


wherein R represent an alkyl group containing up to five carbon atoms, and acid addition salts thereof.

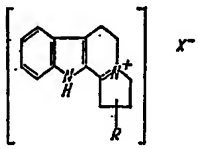
6. Indolo-indolizine compounds according to claim 5 wherein R represents a methyl group.

7. 2,3,5,6,11,11b - Hexahydro - 2 - methyl-1H - indolo [3,2 - g] - indolizine and acid addition salts thereof.

8. Process for the preparation of indolo-indolizines of the formula defined in claim 1 which comprises reacting tryptamine with an ester of a γ-halogenobutyric acid (the halogen substituent being bromine or chlorine), which may carry on one of the carbon atoms of the trimethylene chain an alkyl substituent containing up to five carbon atoms, cyclising the resultant indolylethylpyrrolidone of the formula:



(wherein R is as defined in claim 1) by the Bischler and Napieralski method to a quaternary ammonium compound of the formula:



(wherein X represents the anion of a monobasic acid) and reducing the quaternary ammonium compound thus obtained by treatment with sodium borohydride to an indolo-indolizine of the formula defined in claim 1.

9. Process according to claim 8 wherein tryptamine is reacted with an alkyl ester of γ-bromobutyric acid.

10. Process according to claim 8 or 9 wherein the reaction of tryptamine with the ester of the γ-halogenobutyric acid is effected in an inert organic solvent in the presence of a basic condensing agent.

11. Process according to claim 8, 9 or 10 wherein cyclisation of the indolylethylpyrrolidone is effected by means of phosphorus oxychloride.

12. Process for the preparation of indolo-indolizines of the formula defined in claim 1 substantially as hereinbefore described with especial reference to any one of Examples II to V.

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